Cancer-associated ischemic stroke

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In ischemic stroke patients, the incidence of prior cancer can be up to 16%,[1] both diseases causing significant disability and loss of productive life-years. In a recent US-based nationwide registry study, about 10% of all hospitalized ischemic stroke patients had comorbid cancer, with a slight rise in this rate over the last decade.[2] Stroke patients diagnosed with occult cancer are usually older with men being at a higher risk of having comorbid cancer.[3,4] In addition, probability of cancer diagnosis after stroke is associated with smoking, elevated D-dimer, elevated C-reactive protein (CRP), and anemia on admission.[3,4] In a Swedish nationwide follow-up study, patients with cancer developed ischemic stroke 2.2 times more often than their age-and sex-matched non-cancer control population during a six months follow-up. Although the risk of stroke decreased rapidly, it remained elevated even over 10 years.[5] A Danish registry-based case-control study with over 264,000 cancer patients also showed an approximately 2-fold risk for ischemic stroke in occult cancers.[6] No solid data exist on exact prevalence of different cancer types in ischemic stroke patients. However, lung, pancreatic and colorectal cancers seem to have a higher association with ischemic stroke, perhaps due to their aggressiveness.[7] Other reported common cancer types include breast, urogenital and prostate cancers.[7]

Cancer and ischemic stroke share multiple common risk factors such as age, obesity, and smoking. Thus, cancer patients are not immune to common causes of ischemic stroke such as atrial fibrillation, large-artery atherosclerosis and small-vessel occlusions. Despite that, up to 50% of ischemic strokes occurring in patients harboring a cancer are considered cryptogenic. However, these strokes usually have an embolic pattern and it has been suspected that they are actually cardioembolic manifestations of cancer-mediated hypercoagulopathy or even caused by a paradoxical embolism.[8] Cancer can also cause marantic (non-bacterial) endocarditis, mechanical compression of critical vessels, anemia, and tumor embolism.[8,9] Other potential mechanisms that increase the risk of ischemic stroke in the presence of cancer include endothelium dysfunction and abnormalities in turbulence in abnormal blood vessels. It is essential to keep in mind that also cancer treatments, such as surgery, radiotherapy, and chemotherapy, can increase the risk of subsequent stroke by leading to thrombin generation, embolism, and radiation-induced vasculopathy.[8,9]

In cancer-associated ischemic stroke, several factors, such as elevated D-dimer and specific cancer types (especially adenocarcinomas) are also associated with an increased early neurologic

deterioration, recurrent strokes and other types of thromboembolism.[10-12] Furthermore, ischemic stroke patients with active cancer have a higher risk for both short-term and long-term mortality. This risk is even higher in cancer patients with severe strokes, metastases, diabetes, elevated CRP and higher D-dimer levels.[8]

Hence, patients harboring an active cancer and admitted with an acute stroke is a common scenario. In this issue of Acta Neurologica Scandinavica, Tybjerg and colleagues investigated the prevalence and risk of occult cancer in stroke by using national registries in Denmark.[13] They identified all patients >40 years old with either ischemic or hemorrhagic stroke from their national stroke registry and matched them to the general Danish population with a 1:10 ratio (approximately 86,000 stroke patients and 860,000 stroke-free control subjects). Linking to a national cancer registry, they found that cancer prevalence (per 1,000) was clearly higher among stroke patients: stroke vs. background population 25.0/15.8 in women and 29.8/20.4 in men. As in prior studies, the prevalence of cancer was highest in the oldest patients aged over 70 years (35.6 in women and 42.4 in men per 1,000). Risk of occult cancer was 54% higher in stroke patients, increasing further with age, male gender, smoking, and diabetes. This study brings an interesting addition to the current body of evidence, providing useful data on numbers needed to screen (NNS) cancer in stroke patients. NNS in order to detect cancer in these stroke patients was 40 for women and 34 for men compared to the stroke-free background population, NNS 63 for women and 49 for men.[13]

A relevant question is whether to search for an underlying cancer in the first place in a stroke patient and which cancers are worth searching for first. No international guideline included a recommendation on this topic yet. A suspicion of cancer-associated ischemic stroke should be raised especially in patients with a stroke of undetermined source, persistently elevated markers of coagulation (most notably D-dimer), weight loss, active smoking or history of smoking, fatigue, anemia, elevated CRP and/or erythrocyte sedimentation rate (ESR), low hematocrit, and patients with embolic stroke pattern in brain imaging.[7] Thus, in a high clinical suspicion of a cancer-associated stroke, etiological investigations could include broad laboratory assessment, including D-dimer levels, as well as whole-body computer tomography imaging and carefully selected tumor markers, such as CA125 and CA199 to exclude lung cancer.[7] If needed, further investigations should include positron emission tomography with the glucose analog 2-[^{18}F]fluoro-2-deoxy-d-glucose (FDG-PET) or in a strong suspicion of colorectal cancer, fecal occult blood

tests and/or colonoscopy with biopsies. However, there is still a clear need for guidelines and a cancer probability score regarding which stroke patients should undergo cancer screening and what the extent of such a screening might be.

Another relevant clinical question is how to manage stroke patients with comorbid cancer to avoid recurrent strokes, both ischemic and hemorrhagic. Thus far, only a few studies have addressed the issue of an optimal secondary prevention in cancer patients with an acute ischemic stroke. The TEACH pilot study of 20 ischemic stroke patients with an active cancer comparing treatment with enoxaparin and aspirin showed that the cumulative rates of thromboembolic events, major bleeding, and survival rates were similar between the treatment arms.[14] Another study with 48 cryptogenic ischemic stroke patients with an active cancer, that compared new oral anticoagulants and low-molecular weight heparin in secondary prevention, showed similar clinical outcomes and safety between the two groups.[15] In an exploratory analysis of the NAVIGATE ESUS trial, among 7213 randomized patients with an embolic stroke of undetermined source, 543 (7.5%) reported a history of cancer. Of these, 254 were randomized to rivaroxaban and 289 to aspirin. Both treatment arms had similar risk of recurrent ischemic stroke and all-cause mortality, but aspirin seemed safer than rivaroxaban regarding major bleeding, consistent with the overall trial results.[16] Larger prospective randomized trials comparing safety and efficacy of various anticoagulant and antiplatelet agents are warranted.

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